JTD JOURNAL OF THORACIC DISEASE
A PEER-REVIEWED, OPEN ACCESS JOURNAL FOR HIGH-QUALITY RESEARCH IN THORACIC DISEASES
IMPACT FACTOR 2.895

Peer Review File

Article information: https://dx.doi.org/10.21037/jtd-21-1532

Reviewer A

I am very impressed with your successful clinical diagnostic algorithm for tuberculous pleural effusion (TPE) and long-term follow-up. I have several points to be concerned about.

1) *It is well known that the most common causes of pleural effusion are congestive heart failure, cancer, pneumonia, and pulmonary embolism. But the pulmonary infection was only 6.17% in Fig 5.*

Reply: We have noticed some previous studies and totally agree with your concerns. We consider that the difference may attribute to that our study only enrolled patients with unilateral pleural effusion but not patients with bilateral pleural effusion.

2) *The results of 3 tests (PPD test, IGRA test, TB-Ab test) were so inconsistent, so the usefulness of these tests could be doubtful. How many participants who have exudative pleural effusion with elevated ADA level (>40 U/L) were classified into other causes (393 cases) among malignant pleural effusion, tuberculous pleural effusion, and other causes? The ages of patients with TPE were relatively young (mean 41 years), so primary TB infection could explain the negative results of 3 tests).*

Reply: According to our knowledge and clinical experiences, we all agree that the usefulness of the three tests is indeed very limited. Positive results are just indications for doctors, and the exact diagnosis should be determined combined with other tests. That's why we conducted this study. Besides, the relatively young patients make it hard to get positive results of the three tests. In this study we focused on patients with exudative pleural effusion with elevated ADA level and with one positive results of the three tests, defined as patients of clinical diagnosis. For participants who have exudative pleural effusion with elevated ADA level, we re-calculated all the patients. The results were as follows: **127 cases with tuberculous pleural effusion, 4 cases with malignant pleural effusion and 10 with other causes**.

3) p 10 line 190--191: Why did the patients with TPE receive a thorough closed thoracic drainage? Was that subjected to anti-TB procedure?

Reply: Thoracic drainage is controversial in TPE treatment. As far as we know, some think that it's necessary to perform thoracentesis as soon as possible (*Shaw, JA, Diacon, AH, Koegelenberg, CFN. Tuberculous pleural effusion. Respirology. 2019; 24: 962–971.And Zhai K, Lu Y, Shi HZ. Tuberculous pleural effusion. J Thorac Dis. 2016;8(7):E486-E494*). But some study showed that the addition of pigtail drainage to an effective anti-TB regimen might not be beneficial in TPE treatment (Lai Y, Chao T, Wang Y, et al. Pigtail drainage in the treatment of tuberculous pleural effusions: a randomised study. Thorax 2003;58:149-151). In China, the clinical pathway for TPE treatment required a closed thoracic drainage, so all patients in our study received this procedure before anti-TB drugs procedure. http://www.nhc.gov.cn/yzygj/s7659/202001/b3c9e097b0c1471a969d7a63be471759.shtml(visit at 2021.11.03)

4) p19 line 412: analysis--> should be corrected as analysis

Reply: We apologize for the mistake and have corrected it. Changes in the text: p19 line 436

Reviewer B

Yu and co-workers retrospectively examined the value of 5 non-invasive tests (ADA + PPD, MTB antibody, IGRA and/or pathology/DNA/smear/culture) in diagnosing pleural effusion due to TB.

Comments

1) They had 36 patients with confirmed TB and 203 with "clinically diagnosed" TB giving a total of 239 cases. This is where it gets confusing for me. They say 187 were followed for 1 year but later they say 218 patients were diagnosed with "clinical TPE" = 36 confirmed cases + 182 successfully treated. I think a flow diagram showing the different subgroups would be very helpful here for the reader.

Reply: We apologize for not making it clear. The 239 cases were clinical diagnosed cases, of which 187 receiving over 1-year follow-up. After 1-year treatment, 182 cases were finally confirmed. So, there were a total of 218 correctly diagnosed cases.

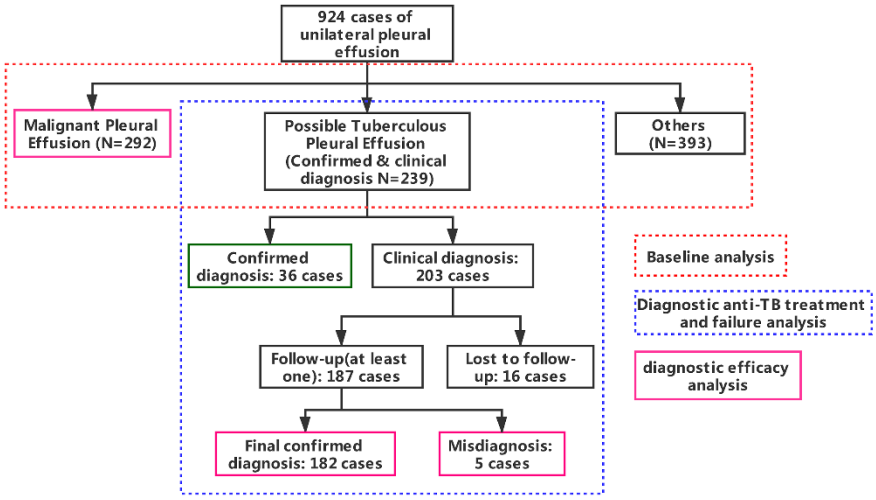

Figure 1 gave the flow diagram of this study.

2) *The abstract needs to reflect the key methods better. No mention is made of the 5 tests employed.*

Reply: Thank you for your suggestion and we have revised our abstract accordingly.

Changes in the text: p3 line 38-42

3) *Do they have the drug susceptibility profiles of the patients with confirmed TB since they all seem to have received the standard regimen for drug-susceptible TB?*

Reply: We have to say that none of them received drug susceptibility tests until the first-line anti-TB regimens was not working. Besides, only specialist hospital for infectious diseases and few advanced hospitals could carry out this test, not even for most of the tertiary hospitals. This is another reason why we conducted this study, providing a reference for some basic hospitals.

4) *Can the authors be more direct on which tests they would recommend? Based on Figure 4, ADA alone seems very good. What other tests combined with ADA gives further improvement in accuracy? Perhaps ADA and IGRA combined provides the best balance of excellent accuracy and not doing all 5 tests? PPD is not specific for active TB, especially in a country with (universal) BCG vaccinations. It is unlikely that most places will be able to do TB antibody so if it is not needed to further improve accuracy, should perhaps say that.*

Reply: This is definitely an important question. From our data, ADA did perform well enough in differentiating TPE form MPE. But this is based on the exudate

characteristic of the effusion. There were still some TPE patients with transudate and positive microbiological/pathological/molecular tests, and patients of other causes with exudate and positive ADA. Due to this fact, our diagnostic algorithm includes three levels. The first is any one positive result of microbiological, pathological or molecular tests, indicating the confirmed cases. The second level is exudate and elevated level of ADA with any one positive result of immunoassay, indicating clinical diagnosed cases. The third level is just exudate and elevated level of ADA, indicating suspected cases. Patients in the first two levels were subjected to anti-TB therapy and follow-up, while patients in the third level were further analyzed by doctors. As for PPD and TB-Ab, they were still recommended as complement because of the cheap prices.

5) *In the "Diagnostic criteria" section, they mentioned ADA + 3 other tests but not the pathology/DNA/smear/culture shown in Figure 3? Also, they mentioned that "confirmation of TB was defined as either one of the following: (1) presence of PE based on image examination and pathological evidence (granulomatous inflammation with or without [antacid] stain smear positive or PCR positive from PE or pleura; (2) presence of PE and microbiologic evidence…". {[antacid] should be "acid-fast". What if the AFB and PCR were both negative? Also please clarify sentence as you cannot make a granulomatous inflammation from the PE.*

Reply: Thank you for your great suggestion and we have revised corresponding contents. Changes in the text: p7 line 135-137, p8 line 154-156 158-160 165-167. If the AFB, PCR, microbiological tests and pathology were all negative but one of immunoassay was positive, this patient would be classified as clinical diagnosis, then entered the empiric anti-TB therapy procedure.

6) *While I am impressed with the writing by a group of individuals with (I assume) English not being their primary language, I think the writing can be significantly improved. For example, in the Abstract and other places, the term "Diagnostic treatment" is used. I'm not sure what this means. Do they mean "Empiric treatment" or perhaps something else? In Introduction (lines 63-64 should read:….diagnosing a precise cause of PE is important), Introduction (line 73: … culture media delays the precise diagnosis…Hence, more ….).*

Reply: We sincerely accept your suggestion and have asked a native speaker to revise our manuscript. Changes in the text: p3 line 32-35, 54; p4 line 66-67, 76-77. Other changes were also made and marked in red.

Reviewer C

The work is well done among patients with PE and reviewed the causes of PE. However, diagnosis of TPE without having culture and/or pathology has been well established. Particularly, in the country where TB is prevalent, any kind of PE should be suspected of TPE. And if ADA is over 40 without any other reason, possibility of TPE is very high. Courtiers like Korea, official guideline recommends ADA to be the diagnostic criteria of TPE unless other etiology is found. Reviewing hundreds of medical records retrospectively is a big job. I really respect the laborious trial. However, reviewer can not find something new regarding Dx of TPE compared to other studies published so far. As far as ADA is concerned, it is more than 30 years since ADA is recommended as an important parameter in the diagnosis of TB pleural effusion(TPE). If authors try again in a prospective manner, maybe the study could be of value. And it could reflect different situation in study group. IGRA is not a good indicator of current TPE since it also reflects past infection of TB, which can not differentiate present vs past infection. Also routine sputum examination is highly recommended even if CXR finding shows no definitive infiltration. Routine sputum examination should include sputum induction because there some data on the role of induced sputum on Dx of TPE. When you try prospective study, routine examination of sputum AFB should be also included to make your study more perfect.

Reply: Thank you very much for your important suggestion. Retrospective design is indeed the biggest limitation of this study, and further prospective study will be conducted. As for ADA, we also showed its good efficacy in TPE diagnosis. But our main aim in this study is to evaluate the algorithm newly put into effect since 2018 in China in the diagnosis of TPE. The data showed satisfying results, which proved the effectiveness of this algorithm. However, as the reviewer said, no new diagnostic method was listed in this study. Further prospective design is needed to specify different situations in TPE diagnosis. Besides, this algorithm is also established based on ADA. If a patient with elevated level of ADA and exudate effusion, he/she is also

classified as a suspected TPE cases. However, our study failed to enrolled this group of patients. Further prospective design will also include this analysis. As far as other immunoassays were concerned, they were all complements to IGRA. PPD, TB-Ab tests were cheap in price, so they were also recommended in this algorithm.

Reviewer D

Authors have submitted an algorithm for the diagnosis of TPE that could be used in the clinical setting, but as with all retrospective studies, the limitations should be discussed.

Reply: Thank you for your suggestions and we have added some limitations in discussion part. Changes in the text: p15 line 325-328.

1) *line 173: ?typo*
   ...the TPE group had a larger proportion of smoking patients than TPE group (P<0.001).

Reply: We apologize for the mistake and have corrected it. Changes in the text: p10 line 186.

2) *The mean LOS was more than 2 weeks for both TPE and MPE groups. This seems rather long for the workup of pleural effusions. Could the authors explain?*

Reply: In our department, after TPE diagnosis was determined, the anti-TB procedure would start immediately. However, patients were still asked to stay for 1 week, so that doctors could monitor the side effects of anti-TB drugs, especially liver function. Likewise, after MPE diagnosis was made, patients were asked to start the anti-cancer therapy. As a result, the LOS was relatively long in this study.

3) *Of the 10 patients who were incorrectly diagnosed with TPE using the author's algorithm, 2 had cancer (angiosarcoma and lymphoma), and both were IGRA negative. IGRAs have been shown to perform better than PPD and TB-Ab test in supporting the diagnosis of TB. Authors should consider performing a similar study prospectively with just IGRA to validate their results.*

Reply: We totally agree with you. From our retrospective data, we also found that the IGRAs performed better than PPD and TB-Ab test in diagnosis of TPE. However, not

all patients received all the 3 tests. There were only 22 TPE patients with TB-Ab test positive but 126 TPE patients with IGRAs positive. A prospective study including IGRA efficacy has been conducted now, and we hope to finish it soon.

4) *line 310: I think this recommendation is too strong based on this retrospective study*

   ...suspected TPE patients, and should be implemented in regions of high TB prevalence.

   There were 5 treatment failures with the algorithm due to drug resistance. As such it would be prudent not to use his algorithm in countries with high drug resistance to 1st line anti-TB medications.

Reply: Thank you for your suggestions and we have corrected the recommendations. We admit that drug resistance tests were not available in this study. In the following prospective study, drug resistance tests will be part of our study design. Changes in the text: p15 line 317-318

Reviewer E

The study "Clinical Diagnostic Algorithm in Defining Tuberculous Unilateral Pleural Effusion in High Tuberculosis Burden Area Short of Diagnostic Tools" is relevant, but currently the therapeutic test is little accepted, since we have laboratory methods at low cost for the presumptive diagnosis of pleural Tb, such as the association of lymphocytic pleural effusion with high protein content and high ADA.

Reply: We apologize for not making it clear about therapeutic test. In this study, therapeutic test referred to the anti-TB therapy only when there is no positive result for neither molecular, pathological or microbiological test. However, exudate and high ADA level along with a positive immunoassay were still the requirements before we started the anti-TB therapy.